Remarks

Claims 42-62 were pending in the subject application. By this Amendment, claims 42-62 have been cancelled and claims 63-89 have been added. The undersigned avers that no new matter is introduced by this amendment. Accordingly, claims 63-89 are currently before the Examiner for consideration and favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. 1.114 for the subject application. Also submitted herewith is an Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

The applicant and the applicant's representative wish to thank Examiner Afremova and Examiner Saucier for the courtesy of the telephonic interviews conducted with the undersigned on January 8, 2004, February 3, 2004, and February 11, 2004, regarding the rejections under 35 U.S.C. §112, first and second paragraphs, and the prior art rejections under 35 U.S.C. §102(b) and §103(a). The remarks and amendments set forth herein are consistent with the substance of the interviews and are believed to address the outstanding issues as discussed during the interviews.

The applicant gratefully acknowledges the Examiner's withdrawal of the prior art rejections based on Pittenger *et al.* and U.S. Patent No. 6,010,696.

By this Amendment, the applicants have cancelled claims 42-62 and added claims 63-89. Claims 63-89 recite that the pluri-differentiated mesenchymal progenitor cells are not cells of a cell line. Support for new claims 63-66 and 73-76 can be found, for example, at page 2, lines 6-12, page 11, lines 27-30, page 12, lines 4-7, page 13, lines 19-31, page 15, lines 1-2, page 16, lines 1-7, page 26, lines 20-25, page 27, lines 28-33, page 28, lines 4-33 (Table 1), page 29, lines 1-16, page 31, lines 15-33, and page 32, lines 11-28, of the specification as originally filed. Support for new claims 67, 68, 77, and 78 can be found, for example, at page 32, lines 30-33, and page 33, lines 1-2, of the specification as originally filed. Support for new claims 69 and 79 can be found, for example, at page 20, line 30, of the specification. Support for new claims 70-72 and 80-82 can be found, for example, at page 6, lines 1-5, page 13, lines 19-31, and page 16, lines 9-33. Support for new claims

83-85 can be found, for example, at page 5, lines 26-33, page 6, page 7, lines 1-20, and pages 17-22, of the specification and the claims as originally filed. Support for new claim 86 can be found, for example, at page 21, lines 25-34, and page 22, lines 1-11, of the specification. Support for new claims 87-89 can be found, for example, at page at page 2, lines 6-12, page 8, lines 5-7, page 11, lines 27-30, page 12, lines 4-7, page 13, lines 19-31, page 15, lines 1-2, page 16, lines 1-26, page 17, lines 1-7, page 26, lines 20-25, page 27, lines 28-33, page 28, lines 4-33 (Table 1), page 29, lines 1-16, page 31, lines 15-33, and page 32, lines 11-28, of the specification as originally filed.

Claims 50-62 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicant respectfully submits that the subject specification provides an adequate written description of the claimed subject matter.

The Office Action states that the specification does not provide support for the concept that "each" cell or "at least 95%" of the cells simultaneously express a plurality of genes that are markers for multiple cell lineages comprising at least four different mesenchymal cell lineages, such as adipocyte, osteoblast, fibroblast, and muscle cell. The applicants respectfully submit that the specification would convey to one of ordinary skill in the art that the applicant was in possession of the claimed subject matter at the time the application was filed.

Submitted herewith for the Examiner's consideration is a Declaration under 37 C.F.R. §1.132 by Dr. Beerelli Seshi. As acknowledged at page 3 of the Office Action, 85% of the cells tested expressed the fourth mesenchymal cell lineage marker, the muscle cell marker actin. However, the pluri-differentiated mesenchymal progenitor cells of the invention express other muscle-specific markers, such as caldesmon and transgelin, as determined by Northern blot analysis and as described at page 9, lines 20-21, and page 32, lines 11-15, of the subject specification. As indicated at page 32, lines 24-27, of the specification, the morphologic, cytochemical and immunohistochemical results, and the Northern blot data disclosed in the specification, the cells of the present invention co-express markers specific for at least four different mesenchymal cell lineages. Therefore, as indicated by Dr. Seshi, "the cells of the invention express the full spectrum of mesenchymal cell markers recited in the claims, and the cells are homogenous in this regard."

Furthermore, as described at pages 15 and 16 of the patent application, the pluri-differentiated mesenchymal progenitor cells of the subject invention were isolated from Dexter

culture such that they were 95% free of macrophages and hematopoietic cells. However, as Dr. Seshi states in the Declaration, "it would be immediately envisioned by those of ordinary skill in the art that the remaining 5% of contaminating cells (macrophages and hematopoietic cells) could be removed using methods known in the art, such as immunomagnetic separation (IMS) techniques, thereby achieving a purity of greater than 99%." IMS has been utilized to separate and enrich cells from bone marrow and peripheral blood for some time (Naume *et al.*, 1997, *J. Hematother.*, 6(2):103-114; Naume *et al.*, 1998, *Int. J. Cancer*, 78(5):556-560; Shibata, K. *et al.*, 1998, *Int. J. Oncol.*, 12(6):1333-1338). The abstracts of Naume *et al.* (1997), Naume *et al.* (1998), and Shibata *et al.* (1998) are submitted herewith.

Given the standard for written description under 35 U.S.C. §112, first paragraph, the applicant cannot find proper context for the Examiner's statement at page 3 of the Office Action that "this is a matter of written description, not a question of what one of skill in the art would or would not have known". As the Examiner is aware, the fundamental factual inquiry for written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicant was in possession of the invention as claimed. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ 2d 1111, 1116 (Fed. Cir. 1991) and MPEP §2163. Thus, the determination of whether the applicant was in possession of the claimed invention is made from the perspective of one skilled in the art and the knowledge of one skilled in the art is clearly relevant. Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the description. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986). Furthermore, while the applicant acknowledges that a later-dated publication cannot supplement an insufficient disclosure in a prior-dated application, the applicant respectfully submits that post-filing date publications are proper when they are offered to show what the specification would convey to those of ordinary skill in the art as of the filing date.

The experimental data disclosed in the subject specification is described in the Seshi *et al.* (2000) publication (*Blood Cells, Molecules, and Diseases*, 26(3):234-246), which was submitted with the Information Disclosure Statement filed August 28, 2003. Dr. Seshi's findings concerning

the pluri-differentiation exhibited by the mesenchymal progenitor cells of the present invention has been acknowledged within the scientific community, as demonstrated by subsequent publications that reference this work, such as Siler *et al.* (see page 219, first column, lines 4) and Woodbury *et al.* (see page 915, second column, 22-34), which are submitted with the IDS that accompanies this Amendment.

The fact that the pluri-differentiated mesenchymal progenitor cells of the invention express four lineage-specific mesenchymal cell markers, including muscle cell markers, was also confirmed in the Seshi *et al.* (2003) publication (*Blood Cells, Molecules, and Diseases*, 31:268-285), which is submitted with the IDS accompanying this Amendment. The Seshi *et al.* (2003) publication describes microarray analysis of the mesenchymal progenitor cells of the invention at the single-cell level. Dr. Seshi states in his Declaration,

> [a]s shown in the gene expression plots of Figures 6A and 6B, and as outlined in Table 2 (A-D) of the Seshi *et al.* (2003) publication, isolated single cells simultaneously expressed genes specific for four different mesenchymal cell lineages (osteoblast, muscle, fibroblast, and adipocyte). Figure 6A of the publication shows that all ten single-cell samples expressed both muscle cell markers caldesmon and transgelin. These results support the concept that each of the mesenchymal progenitor cells of the invention express the full repertoire of mesenchymal cell markers recited in the claims (*i.e.*, at least four different mesenchymal cell lineages, wherein each of the markers is specific for a single cell lineage). Because this feature can be reasonably attributed to each of the cells, they are homogenous in this regard.

(Seshi Declaration, page 3, lines 5-14).

Each cell expresses genes specific for different mesenchymal cell lineages, as recited in the claims. Accordingly, in view of the foregoing remarks, the applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claim 56 has been rejected under 35 U.S.C. §112, second paragraph, as indefinite. The applicant respectfully submits that the term "isolated" does not render the claim indefinite. However, as indicated above, by this Amendment, the applicant has cancelled claim 56, rendering this rejection moot. New claims 63, 73, 87, and 89 recite that the pluri-differentiated mesenchymal progenitor cells are isolated. Unless otherwise specified, the term "isolated" is used in its ordinary and customary meaning as interpreted in the instant Office Action, *i.e.*, derived and/or separated from other bone marrow cells. Isolation of the pluri-differentiated mesenchymal progenitor cells of

the present invention from macrophages and hematopoietic cells is described, for example, at page 16, lines 9-33, and page 17, lines 1-6, of the subject specification. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 42-62 have been rejected under 35 U.S.C. §102(b) as being anticipated by Torok-Storb *et al.* (U.S. Patent No. 5,879,940). The applicant respectfully submits that the Torok-Storb *et al.* patent does not teach or suggest the cells of the subject invention.

As indicated above, the applicant has cancelled claims 42-62 and added claims 63-89. New claims 63-89 recite that the pluri-differentiated cells are not cells of a cell line. As explained by Dr. Seshi in the Declaration, there are only three types of cells in Dexter-type cultures (also known as long-term marrow cultures (LTMC)): macrophages, hematopoietic cells, and the non-hematopoietic cells of the present invention, which simultaneously express marker genes specific for multiple mesenchymal cell lineages, including adipocytes, osteoblasts, fibroblasts, and smooth muscle cells. Prior to this, the prevailing belief was that stromal cells of Dexter-type cultures were a heterogenous mixture of adipocytes, osteoblasts, fibroblasts, muscle cells, and vascular endothelial cells. Thus, the cells of the present invention are obtainable from primary Dexter-type cell cultures and simultaneously express a plurality of genes that are markers for multiple cell lineages without the need for genetic modification.

In contrast to the cells of the present invention, the Torok-Storb *et al.* patent describes several bone marrow stromal cell lines that have been transformed with human papilloma virus (HPV). Dr. Seshi notes at page 4 in his Declaration: "[a]lthough the cells of the Torok-Storb *et al.* patent and the cells of the present invention both originate from Dexter-type cultures (as prepared in Gartner and Kaplan, *Blood* 56:117, 1980), that is where their similarity ends." As described at column 11, lines 38-65, of the Torok-Storb *et al.* patent, LTMC (Dexter-type cultures) were established. The LTMC are a heterogeneous mixture of macrophages, hematopoietic cells, and non-hematopoietic cells, as taught in the subject specification. Next, the primary LTMC were immortalized with HPV and transduced clones were selected and expanded, resulting in the immortalized stromal cell lines of the Torok-Storb *et al.* patent (see column 11, lines 60-62). In contrast, the pluri-differentiated cells of the present invention were isolated from primary cultures (Dexter-type cultures) by removal of hematopoietic cells and macrophages, as described at page 16, lines 11-33, of the subject

specification, and subsequently characterized. Thus, "[n]o immortalization or other genetic modification was undertaken" (Seshi Declaration, page 4).

The immortalized stromal cell lines of the Torok-Storb *et al.* patent were qualitatively analyzed by immunocytochemistry. The applicant respectfully submits that the Torok-Storb *et al.* patent does not indicate that any of the cells of the immortalized cell lines simultaneously expresses genes that are markers of at least four different mesenchymal cell lineages, wherein each of the markers is specific for a single cell lineage, as recited in the claims. For sake of clarity, the qualitative results reported by Torok-Storb *et al.* pertaining to the mesenchymal cell markers are summarized in Table A at pages 4-5 of the Seshi Declaration.

As described at columns 13 and 14 of the Torok-Storb *et al.* patent and summarized in Table A of the Seshi Declaration, four cell lines (HS-5, HS-21, HS-23, and HS-27) were qualitatively tested for the expression of a variety of markers. Only four of the markers tested are mesenchymal markers that are specific for a single cell lineage, as recited in the claims of the subject application. These are the muscle marker actin, the fibroblast marker fibronectin, the osteoblast marker alkaline phosphatase, and the adipocyte marker Oil Red O. As explained by Dr. Seshi, "it should be understood that the markers vimentin, Collagen I, Collagen II, and Collagen III, for example, are each specific for a variety of mesenchymal cell lineages, such as lymphoid cells, fibroblasts, endothelial cells, and smooth muscle cells" (Seshi Declaration, page 5). Therefore, these markers are not specific for a single cell lineage as recited in the claims.

Based on the legend in Table 1 of the Torok-Storb *et al.* patent, all four cell lines were "strongly positive" for the muscle marker actin, and showed "good staining" for the fibroblast marker fibronectin. However, the cells of the HS-5 cell line did not express the markers specific for osteoblasts (Table 1) or adipocytes (column 14, lines 43-44). Furthermore, the cells of the HS-21 cell line were only "heterogeneously positive" for the osteoblast marker (Table 1), and did not express the marker for adipocytes (column 14, lines 43-44). Thus, as Dr. Seshi concludes "[c]learly, the cells of the HS-5 cell line and HS-21 cell line do not simultaneously express markers of least four different mesenchymal cell lineages, wherein each marker is specific for a single cell lineage" (Seshi Declaration, page 5).

The Torok-Storb *et al.* patent indicates that cells of the HS-23 cell line were only "heterogeneously positive" for the osteoblast marker (Table 1) and formed lipid vacuoles only in the presence of dexamethasone, but not in the presence of other steroids and not to the extent of the large multilocular vacuoles observed in LTMCs (see column 14, lines 46-51). Likewise, the cells of the HS-27 cell line were only "heterogeneously positive" for the osteoblast marker and "only a few cells (approximately 1-2%)" of the cell line formed lipid vacuoles (see column 14, lines 44-45). The applicant respectfully submits that the qualitative data reported in the Torok-Storb *et al.* patent does not indicate that any cells within the HS-23 or HS-27 cell lines simultaneously express all four markers, as recited in the claims of the subject application. The fact that the cells of the HS-23 and HS-27 cell lines only had "good staining" of the fibroblast marker, were only "heterogeneously positive" for the osteoblast marker, and had very limited expression of the adipocyte marker does not convey to one of ordinary skill in the art that any cells within the cell lines simultaneously expresses these markers. For example, in order for any cells of the HS-27 cell line to simultaneously express all four markers, it would have to be shown that the "few cells (approximately 1-2%)" that formed lipid vacuoles were also among those positive for the osteoblast marker. As stated by Dr. Seshi in the Declaration, "because the cells were only "heterogeneously positive" for the osteoblast marker, cells that were positive for the adipocyte marker and osteoblast marker may be mutually exclusive. Therefore, simultaneous expression of all four markers cannot be attributed to the cells" (Seshi Declaration, page 6).

In contrast to the immortalized cells of Torok-Storb *et al.*, Table 1 of the subject application shows that all of the mesenchymal progenitor cells expressed the adipocyte marker (Nile Red), all of the cells expressed the osteoblast marker (alkaline phosphatase), all of the cells expressed the fibroblast marker (fibronectin and prolyl-4-hydroxylase), and 85% of the cells expressed the muscle marker (actin). Therefore, necessarily, those cells expressing the muscle marker must have also expressed the other three mesenchymal cell markers. This is not the case for the Torok-Storb *et al.* cell lines. Furthermore, as indicated above, the Seshi *et al.* (2003) publication contains experimental data verifying that the cells of the subject invention individually express at least four different mesenchymal-specific cell markers, including an adipocyte marker.

The Examiner appears to rely on the premise that because the cells in the Torok-Storb *et al.* patent are cell lines, the cells within each cell line are homogenous and share the same phenotype. However, as explained by Dr. Seshi in the Declaration, "the intra-cell line heterogeneity in the expression of the markers in Table 1 is inconsistent with this premise. For example, the significant heterogeneity in the expression of the osteoblast and adipocyte markers may suggest non-specific staining (a false-positive), or may indicate that the cell lines are unstable or have lost their monoclonality. This latter possibility is made more likely by Example 1 of the Torok-Storb *et al.* patent itself" (Seshi Declaration, paragraph bridging pages 6 and 7). The Torok-Storb *et al.* patent indicates that Southern hybridization produced autoradiographs with two bands for each of the HS-21 and HS-27 cell lines, "indicating either that they contained two inserts or that two clones contribute to the line" (emphasis added) (see Column 12, lines 53-57, of the Torok-Storb *et al.* patent).

Also submitted with the IDS accompanying this Amendment is the Graf *et al.* publication (*Blood*, 100(4):1509-1511, 2002), which describes gene expression profiling of the HS-5 cell line and HS-27a cell line, a sub-clone of the HS-27 cell line, using DNA microarray technology. The applicants respectfully submit that there is no data within the Graf *et al.* publication indicating that the cells of the HS-27a subclone simultaneously express the four mesenchymal-specific markers tested for in the Torok-Storb *et al.* patent. Therefore, the Graf *et al.* publication does not support the homogeneity of the parent cell line (HS-27).

Based on the heterogeneity in the markers expressed by the cells within each immortalized cell line of the Torok-Storb *et al.* patent, the applicant respectfully submits that one of ordinary skill in the art would not conclude that any one cell simultaneously expresses genes that are markers of at least four different mesenchymal cell lineages, wherein each of the markers is specific for a single cell lineage.

To the extent that the Office Action asserts that the immortalized cells of the Torok-Storb *et al.* patent are characterized by "the same phenotype" as the presently claimed pluri-differentiated cells, the applicant respectfully submits that the presence of inherent matter must be grounded on more than speculation, it must be a certainty. *Ethyl Molded Product Co. v. Betts Package Inc.*, 9 USPQ 2d 1001, 1032-1033 (I.D.KY 1988) ("the doctrine of inherency is available only when the

prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation" (emphasis added)). Furthermore, when the reference is silent about the asserted inherent characteristic, while such a gap in the reference may be filled with recourse to extrinsic evidence, the extrinsic evidence

> must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 49 USPQ 2d 1949, 1950-1951 (Fed. Cir. 1999).

There is no teaching in the Torok-Storb *et al.* patent, nor has the Examiner shown, that it is a certainty that any of the immortalized cell lines in Torok-Storb *et al.* simultaneously express a plurality of genes that are markers for multiple cell lineages comprising at least four different mesenchymal cell lineages (such as adipocyte, osteoblast, fibroblast, or muscle), wherein each of the markers is specific for a single cell lineage. In fact, the scientific literature suggests that the phenotypic characteristics of such immortalized cells are unpredictable. Dr. Seshi notes

> [f]or example, citing Roecklein and Torok-Storb (*Blood*, 85:997-1005, 1995), the Majumdar *et al.* publication, which is relied upon by the Examiner in the instant Office Action, indicates that unpredictable changes in phenotype may occur in immortalized bone marrow stromal cells, such as those immortalized with human papilloma virus E6/E7 genes, which is the same retroviral construct used in the Torok-Storb *et al.* patent (see page 57, paragraph bridging columns 1 and 2 of Majumdar *et al.*; and column 11, lines 56-59, of the Torok-Stork *et al.* patent). (Seshi Declaration, paragraph bridging pages 7 and 8)

The Majumdar *et al.* publication indicates that while immortalized bone marrow stromal cells have been used in long-term bone marrow cultures to further define the heterogeneity in the marrow microenvironment,

> the major disadvantage of relying on transformed and immortalized cell lines to determine the functional elements of the marrow microenvironment lies in the potential of these cells to undergo morphologic, phenotypic, and regulatory changes that make them unpredictable surrogates for their normal cell counterparts (emphasis added).

Also submitted with the IDS accompanying this Amendment is the Roecklein and Torok-Storb *et al.* publication (*Blood*, 85(4):997-1005, 1995), which describes the work on which the

Torok-Storb *et al.* patent is based. As indicated at page 1001, column 2, of the Torok-Storb *et al.* (1995) publication, epithelial cells immortalized by the HPV-16 E6 and E7 genes exhibit aneuploidy (having an abnormal chromosome complement) in late passage cells. The ability of HPV-16 E6 and E7 proteins to induce numerical and structural chromosome instability has been acknowledged elsewhere in the literature, such as Deunsing *et al.* (PNAS, 97(18):10002-10007, 2000) and Deunsing and Munger (Cancer Research, 62:7075-7082, 2002), which are also submitted with the IDS accompanying this Amendment.

Furthermore, the Torok-Storb *et al.* patent does not teach or suggest using the immortalized stromal cell lines as therapeutic agents within a pharmaceutical composition. The Torok-Storb *et al.* patent proposes that the immortalized stromal cell lines be used to sustain and expand hematopoietic precursor cells *in vitro*, where the hematopoietic precursor cells are harvested and subsequently returned to a patient, or frozen and stored (see abstract, column 3, lines 39-42). The Torok-Storb *et al.* patent also states that the immortalized cell lines can be used as feeder layers in *ex vivo* bone marrow cultures or in colony forming assays, or medium conditioned by exposure to the immortalized cell lines may be used *in vivo* to promote hematopoiesis (see abstract, column 3, lines 58-61, and column 4, lines 42-53). The Torok-Storb *et al.* patent does not teach or suggest using the immortalized cell lines in a pharmaceutical composition or otherwise administering the immortalized cell lines to a patient.

At page 6, the Office Action refers to a composition that is a co-culture containing hematopoietic cells and the immortalized stromal cell lines (see column 15, lines 63-67, of the Torok-Storb *et al.* patent). The applicant respectfully submits that while "serum-deprived medium" may be considered a "carrier" in its broadest sense, it is not necessarily a "pharmaceutically acceptable" carrier, as recited in the claims, absent a description of its ingredients. Furthermore, as stated by Dr. Seshi in his Declaration, "the mere fact that the co-culture was observed to support the growth of hematopoietic cells *in vitro* does not necessarily correlate with an amount of cells effective for treating a disease state *in vivo*, for enhancing hematopoietic stem cell engraftment, or for treating graft-versus-host disease" (Seshi Declaration, page 9). As indicated above, in order to anticipate, the presence of inherent matter must be grounded on more than speculation, it must be a certainty. (*Ethyl Molded Product Co. v. Betts Package Inc., supra*).

The applicant respectfully submits that the cited reference does not teach the pluri-differentiated cells or pharmaceutical compositions of the present invention as currently claimed. Accordingly, in view of the foregoing remarks and the amendments to the claims, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claims 42-62 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Majumdar *et al.* (*J. Cell. Physiol.*, 1998, 176:57-66) taken with Torok-Storb *et al.* (U.S. Patent No. 5,879,940) and Bordignon *et al.* (*Haematologica*, 1999, 84:1110-1149). The applicant respectfully traverses and submits that the cited references do not teach or suggest the claimed invention.

In regard to the Torok-Storb *et al.* patent, the applicant hereby incorporates and reasserts the remarks concerning this reference as set forth in response to the above rejection under 35 U.S.C. §102(b). The Office Action indicates that the mesenchymal progenitor cells of the primary reference, Majumdar *et al.*, are of the "same cell population" as Torok-Storb *et al.* and are, therefore, capable of simultaneously expressing four different mesenchymal cell lineages including adipocyte, osteoblast, fibroblast, and muscle cells. However, as indicated above, based upon the heterogeneity in the markers expressed by the immortalized cells within each cell line of Torok-Storb *et al.*, one of ordinary skill in the art would not conclude that any of the cells simultaneously expresses genes that are markers of at least four different mesenchymal cell lineages, wherein each of the markers is specific for a single cell lineage, as recited in the claims. Furthermore, Majumdar *et al.* teach that the immortalized cells of the Torok-Storb *et al.* patent are "unpredictable surrogates" for their normal cell counterparts (see page 57, paragraph bridging columns 1 and 2 of Majumdar *et al*). Thus, the applicant respectfully submits that one of ordinary skill in the art would not consider the immortalized cells of the Torok-Storb *et al.* patent to be of the "same cell population" as Majumdar *et al.*

As explained by Dr. Seshi in his Declaration, prior to his discovery to the contrary, the prevailing belief was that stromal cells of Dexter-type cultures were a heterogenous mixture of adipocytes, osteoblasts, fibroblasts, muscle cells, and vascular endothelial cells. The pluri-differentiated mesenchymal progenitor cells of the subject invention have not previously been isolated or characterized. Dr. Seshi states

> as a result of this perceived cellular complexity, research efforts in the preceding years were not directed to characterizing or isolating the pluri-differentiated

mesenchymal progenitor cells from the Dexter-type cultures. As indicated at page 14, lines 7-23, of the patent application, almost all of the published studies on Dexter-type cultures involved cytochemical and immunocytochemical staining on layers of stromal cells grown to confluence on coverslips. In this "cobblestone" arrangement, the cells appear very complex, with the macrophages and non-hematopoietic cells spreading and assuming various shapes, preventing a clear morphological visualization or characterization of the cells for any particular marker. Only rarely have investigators prepared a cell suspension of Dexter-type cultures and stained the cells on cytospins, as described in Simmons *et al.* (*Nature*, 1987, 328:429-432). Although these methods allow visualization of individual cells, the resulting cytospin preparations still contain the cell types that constitute Dexter-type cultures (*i.e.*, macrophages, hematopoietic cells, and pluri-differentiated mesenchymal progenitor cells). At the time, Simmons *et al.* observed a predominance of two distinct cell populations in the cytospin preparations: macrophages and more heterogeneous appearing cells which they deemed "stromal cells", as discussed at page 429 (column 2) and Figure 1 of Simmons *et al.* Thus, the pluri-differentiated mesenchymal progenitor cells of the present invention were not previously isolated or characterized.

Furthermore, the applicant notes that, consistent with the teachings of the subject specification, the traditional marrow-derived stromal cell (MDSC) cultures described by Majumdar *et al.* express hematopoietic and macrophage cell markers (see page 59 column 2, lines 1-39, and Figure 1, of Majumdar *et al.*). The Majumdar *et al.* publication does not teach or suggest isolation of pluri-differentiated cells of the present invention from the MDSC cultures, or their use in pharmaceutical compositions. Likewise, the Bordignon *et al.* publication does not teach or suggest the pluri-differentiated mesenchymal progenitor cells or pharmaceutical compositions of the claimed invention and, thus, does not cure the deficiencies of the other cited references. In fact, the applicant submits that it is unlikely that the immortalized cell lines of the Torok-Storb *et al.* patent would be considered candidates for inclusion within a pharmaceutical composition, given the nature of the immortalizing agent utilized. HPV-16 is a high-risk cancer type and expression of the E6 and E7 HPV oncogenes has been strongly associated with cervical carcinoma.

The applicant respectfully submits that the cited references do not teach or suggest the pluri-differentiated mesenchymal progenitor cells of the present invention or pharmaceutical composition as currently claimed. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachments: Petition and Fee for Extension of Time;
Request for Continued Examination (RCE) under 37 C.F.R. §1.114;
Information Disclosure Statement, including Form PTO/SB/08 and copies of references listed therein;
Declaration under 37 CFR §1.132 by Dr. Seshi;
Naume *et al.*, 1997, *J. Hematother.*, 6(2):103-114 (abstract);
Naume *et al.*, 1998, *Int. J. Cancer*, 78(5):556-560 (abstract);
Shibata, K. *et al.*, 1998, *Int. J. Oncol.*, 12(6):1333-1338 (abstract)